The examiner believes that claim 18 reads on the naturally occurring polypeptide IL-10 because of the "amounting" language. However, the full phrase is "amounting in total up to about 100 amino acids". According to WO93/17698, IL10 is 156 (ID3) or 160 (ID4) amino acids long. Thus, claim 18 seemingly is to a non-naturally occurring fragment of IL-10.

Moreover, claim 18 is further qualified by at least one of conditions (I)-(V), each of which appears to exclude IL-10.

In order to put the issue beyond doubt, we have amended claim 18 to recite "A non-naturally occurring polypeptide, or a polypeptide in at least partially purified form, which is six to about 100 amino acids in length...."

3. Prior Art Issues

3.1. Claims 18-26, 48 and 55 were rejected as anticipated by Vieira. Vieira teaches cDNA clones encoding human IL-10; the ORF encodes a 178 a.a. polypeptide with an 18 a.a. leader; i.e., the mature polypeptide is 160 a.a. There is no disclosure of any fragments.

Thus, for the reasons already discussed in connection with the "Product of Nature" issue, Vieira does not anticipate.

3.2. Claims 18 and 47 were rejected as obvious over Vieira in view of Kent. Kent merely teaches solid phase peptide synthesis. While this is a means of obtaining desired fragments, neither Vieira nor Kent teach that it is desirable to make IL-10 fragments or that SEQ ID NO:1 has any special significance such as would motivate the art to retain it in such fragments.

3.3. Claims 18, 43, 45-46, 49-54, and 61-64 were rejected as obvious over Vieira in view of Van Laethem. Van Laethem teaches the clinical value of full length IL-10, but does not supply motivation to make the claimed fragments.

3.4. Claims 18, 33, 35-38 are rejected as obvious over Vieira in view of Barrett. Barrett teaches cyclization, C-terminal amidation, and N-terminal acylation of peptides at col. 17-19. Barrett's peptides bound the IL-5 receptor, and were

identified by screening, inter alia, biased random peptide libraries (see col. 12, lines 18-29). It is unclear from Barrett's disclosure where any of the bias sequences corresponded to fragments of IL-5.

While Barrett may have provided motivation to modify the N- or C-terminals of Vieira's full-length IL-10, neither reference teaches fragments of IL-10, and indeed Barrett does not even teach fragments of IL-5. At most he teaches that a 12 a.a. peptide which binds a receptor can be useful, but he does not identify these peptides as fragments of a natural agonist protein.

4. Enablement Issues

4.1. The Examiner concedes enablement for the nonapeptides of SEQ ID NOs 1 and 19-22, but not for the shorter (6-8) or larger peptides (even 10 a.a.!) comprising these sequences, or for peptidomimetics.

Two separate questions were raised as to the larger peptides: (1) where in the claimed polypeptide would the recited sequence be located, and (2) what sequence variation would be permitted outside that recited sequence.

The hexapeptide SEQ ID NO:19 (Thr-X_4-Lys-X_5-Arg-X_6) corresponds to the C-terminal of IL-10 (WO93/17698, ID3, AAs 155-160). Similarly SEQ ID NOs: 1 and 22, the nonapeptides, correspond to AAs 152-160 of WO93/17698, ID3.[1] So clearly it is possible for additional amino acids to precede SEQ ID NO:19 without loss of function. The Examiner has not adduced any reason to believe that those additional amino acids must necessarily correspond exactly to the upstream portion of IL-10. Indeed, they differ as between human IL-10 and viral IL-10.

The Examiner's position on enablement appears to be nothing more than a recognition of the mathematical fact that there are a very large number of amino acid sequences of up to about 100

[1] In the viral IL-10 (BCRF1), the last AA of SEQ ID NOs: 1 and 19-22 is omitted.

amino acids length that would include SEQ ID NO:19.

However, the standard of enablement is not whether it would take undue experimentation to make and test all of the possible polypeptides. As explained by In re Angstadt, 190 USPQ 214, 218 (CCPA 1976):

> Appellants have apparently not disclosed every catalyst which will work; they have apparently not disclosed every catalyst which will work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid "literal" infringement of such claims by merely finding another analogous catalyst complex which could be used in "forming hydroperoxides".

The proper inquiry is as to (1) how readily each polypeptide can be made and tested; (2) what percentage of polypeptides which a person skilled in the art would choose to make and test would in fact have activity, and (3) does the claim have a functional limitation excluding inoperative polypeptides.

See In re Bowen, 181 USPQ at 51; In re Skrivan, 166 USPQ 85 (CCPA 1970); In re Goffe, 191 USPQ 429 (CCPA 1976); In re Strahilevitz, 212 USPQ 561 (CCPA 1982); Ex parte Mark, 12 USPQ2d 1904 (BPAI 1989).

The next question is whether addition of amino acids after SEQ ID NO:10 would substantially interfere with activity. It is

not unusual for proteins with C-terminal region binding sites to have functional variants or mutants in which the C-terminal is extended, especially if the extension is small and does not assume a secondary structure. Hence, claim 18 has further been amended to recite that the claimed polypeptide has a C-terminal subsequence consisting essentially of SEQ ID NO:19, i.e., SEQ ID NO:19 must be at or very near to the C-terminal of the claimed polypeptide and any AAs following the SEQ ID NO:19 moiety must not interfere with activity.

New claim 65 drops the "consisting essentially of" language.

New claim 66 further requires that the polypeptides have a length of up to about 20 amino acids, and new claim 67 that the length not exceed 10 amino acids.

Certain of the pending claims further limit the overall length of the polypeptide to "up to 30 amino acids" (claim 23), "up to 20" (claim 24), "up to 15" (claim 25), 10-14 AAs (claim 26), 9 AAs (claim 27), and "up to about 30 amino acids" (claim 22). These necessarily limit the possible variation of the upstream and downstream sequences.

New claim 68 requires that the polypeptide be modified per (I)-(V) from a peptide selected from the group consisting of SEQ ID NOs: 19-22, effectively limiting it to 6-9 residues with certain constraints on those residues.

With regard to the choice of upstream AAs, it is well within ordinary skill in the art to prepare a combinatorial peptide library of the form

$$(Xaa)_n - (SEQ\ ID\ NO:1)$$

If Xaa could be any of the 20 genetically amino acids, then n could readily be at least 6, as 20^6 is 3.2×10^7 which is not an unusual library diversity. (Barrett, USP 5,654,276, cited by the Examiner, describes use of peptide libraries to find peptides which bind the IL-5 receptor.)

Once one or more preferred immediate upstream sequences are determines, the previously screened region may be held constant and a further amino-terminal extension randomized and screened.

Alternatively, the initial value of n may be higher if the Xaa are limited to a subset of the 20 genetically encoded AAs, e.g., the corresponding IL-10 AA and to one or more conservative substitutions (see p. 13-14) therefor. If each Xaa were only two AAs, then the library could screen as many as 30 variable residues simultaneously (2^{30}~10^9). The libraries screened by Barrett all had more then 10^9 members, see col. 12, line 32.

4.2. The Examiner does not specifically explain why the 6-8 a.a. peptides comprising SEQ ID NO:19 should not have activity. It is well known in the art that hexapeptides can have significant binding activity, e.g., many epitopes are of that length. It is incumbent on the Examiner to make out at least a prima facie case that the 6-8 a.a. peptides are not functional. That the Examiner has failed to do.

If the Examiner chooses to maintain the rejection as to the 6-8 amino acid peptides (preferably with at least sufficient reasoning and supporting evidence to establish a prima facie case), the rejection should not be made final, as the original statement of the rejection was incomplete and inadequate.

4.3. Furthermore, the Examiner does not explain why peptidomimetics (claims 40-46) are not enabled. Peptidomimetics are discussed at page 21, line 17 to page 22, line 9. Peptidomimetics were also designed by Barrett, USP 5,654,276. The Examiner has made no showing that these teachings are inadequate.

While Applicants do not have any data on peptidomimetics per se, they have shown that the several of the positions in SEQ ID NO:1 can be replaced by non-genetically encoded amino acids without abolishing IL-10 agonist activity (see attached exhibit).

4.4. Further enablement issues are raised in connection with the method claims. First of all, the examiner disagrees with the recitation of "preventing" (as opposed to "treating") a disease.

The patent law does not require that to support a claim to "preventing a disease", the specification must disclose

successful use of the drug for that purpose. For such a claim to be properly rejected, there must be reasonable basis to doubt efficacy. We are not aware of any reason why a peptide which competitively inhibits a receptor cannot be used to prevent, as well as treat, a disease attributable to excessive activation of that receptor.

At this point it is appropriate to note that the term "prevent" is commonly used in clinical practice to refer to a procedure which statistically reduces the incidence of the disease in the treatment group relative to the control group. Vaccines have been said, for example, to be X% effective in preventing a disease. The term "prevent" does not normally connote absolute effectiveness. (Of course, in any given patient, it is either effective or ineffective).

Moreover, there <u>is</u> evidence of <u>prevention</u>, see Example 13. "Injection of murine IT9302 into rabbits before induced pancreatitis prevented leukopenia" (page 46, lines 6-8), as demonstrated in Fig. 14. Similarly, Example 14 showed that human I9302 had the same prophylactic effect. There is no reason to believe that it could not have additional preventative roles.

Nonetheless, new claim 69 is limited to treatment.

4.5. The Examiner also wishes to limit the disease to those that "involve pro-inflammatory activities" (cp. new claim 70), i.e., IL-8 and TNFα production, monocyte of T-cell migration", or where "IL-8, MCAF, IL-1 are believed to have pathogenic roles" (cp. new claim 72). The Examiner merely asserts a conclusion without defending it in any way.

The Examiner does not expressly discuss, individually, the diseases enumerated in the Markush groups of claims 42 and 56 or in claims 44 and 57-64 or explain which of the enumerated properties of (a)-(j) in claim 49 does not include a pro-inflammatory activity. The Examiner appears to concede enablement for the treatment of pancreatitis.

Support for the enumerated diseases appears in table 2 (pp. 8-9) and references 20-74 and 109.

New claim 71 requires that the disease be IL-10 inhibited, see page 6, line 12.

5. Definiteness Issues

5.1. OA §5a says that the "amounting" limitation does not place an upper or lower limit on the length of the claimed polypeptide, thereby reinforcing the impression that the examiner does not read this limitation as we do. Note that claim 18 has been amended.

5.2. In response to OA §5b, we have amended 18(j) by deleting the "the" before "TNFα", consistent with limitations (a)(IL-8), (b)(IL-8), (c)(IRAP), (d)(lymphocytes), (e)(T-cells), (f)(lymphocytes), (g)(monocytes), (h)(monocytes), (i)(T cells), and (k)(TNFα and IL-8).

3. In claim 47, "optionally" is proper, see Ex parte Cordova, 10 USPQ2d 1949 (BPAI 1989); MPEP §2173.05(h)(III).

Respectfully submitted,

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Enclosure
-Exhibit "Synthetic Analogues" (8 pp)
-Abstract

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